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Award Number: DAMD17-01-1-0750

TITLE: Acquisition of a Magnetic Resonance Imaging System for Research on the Neural Basis of Human Cognition

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REPORT DATE: September 2004

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2004	Final (15 Aug 2001 - 14 Aug 2004)

4. TITLE AND SUBTITLE
Acquisition of a Magnetic Resonance Imaging System for Research on the Neural Basis of Human Cognition

5. FUNDING NUMBERS
DAMD17-01-1-0750

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

From August, 15, 2001 through August 14, 2002 a facility for housing the 3T fMRI unit was constructed, the 3T MRI unit installed and the essential accessory items (stimulus/response computers, digital projection system, eye-tracking system, auditory system) integrated into the MRI system and made operational and initial, high quality human and non-human subject data have been obtained. From August 2002 through August 2003, the BBMI researchers began to put together the complex story of how networks are developed in areas ranging from auditory perception to cognitive control. They studied the neural anatomy of humans, using electrical recordings to explore the time course and connectivity of the network. They also conducted cellular studies of primates and other mammals. From August 2003 through August 2004 we inaugurated our new Center for Mammalian Genetics and recruited new faculty members in that field and in Cognitive Neuroscience. Results from our group were featured in *Science*, *Nature* and *Neuron*. We have continued our progress in the Lewis Center for Neuroimaging, cognitive neuroscience and neuroinformatics and the development of our infrastructure for proteomics and genomics.

14. SUBJECT TERMS
Brain mapping, cognitive neuroscience, evolution, functional and ICONIC grid, mammalian genetics, neuroimaging, neuroinformatics, proteomics, telemedicine

15. NUMBER OF PAGES
25

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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I. Mission

The goal of the Brain Biology and Machine Initiative is to establish a world-leading center linking genomic and proteomics to human cognitive neuroscience research. Toward this overall goals the following steps will be implemented.

1. To establish a 3 Tesla Brain Imaging Center for scanning of human and animals.

2. To order and install high speed computing for the integration of fMRI and EEG signals to provide informatics support to the initiative.

3. To develop a center for genomic and proteomic research by making links between individual researchers and the centralized genomic facility and to order and install a new mass spectrograph for proteomic research.

4. To develop a mammalian genetics center including animal scanning.

5. To perform research that will move toward the vertical integration across many levels of analysis to link work in genomics and proteomics to studies of cognitive neuroscience.

II. Body

2001-2002

In the twelve month period (August, 2001 to August, 2002) the primary accomplishments are the completed construction of the facility for housing the fMRI unit, the delivery and installation of the fMRI unit, the successful integration and implementation of the stimulus response systems, eye-tracking system, subject physiologic monitoring system, the set up of the image analysis laboratory and the RF coil laboratory and the acquisition of initial structural and functional MRI data from human and non-human subjects. All of these were fundamentally necessary steps to reach the level of performing the research studies outlined in the Statement of Work. The MRI unit has been operational since mid-March of 2002 and the other ancillary equipment integrated and operational since late June of 2002.

With respect to the human studies of brain systems and mechanisms, initial human subject images are provided in the appendix. High quality 3-D structural images with good gray-white matter differentiation are routinely obtainable with the 3T system (see Figure 1). These structural images typically have 1 millimeter isotropic resolution. Structural images (2-D) with a so-called 'T2' contrast are also routinely obtainable with an in-plane resolution of 500 microns (see Figure 2). High definition MR 'angiograms' are also feasible with the system and can be used to map larger blood vessel locations to remove potential contributions of such vessels to the fMRI results (see Figure 3). Functional MRI data from both somatosensory tasks (finger tapping for example) and purely cognitive tasks (solving arithmetic calculations versus recalling lyrics to songs) have been obtained on a regular basis (see Figure 4).

With regard to the animal studies for auditory and visual processing, three custom-designed RF coils have been built and tested. Images from the coil designed for studies in the owl are provided (see Figure 5) and initial images from primates using the 3T MRI unit are also include in the appendix (see Figure 6).

An additional four pages of pictures are provided in the appendix showing the construction, system installation and set-up of the MRI system. Also a picture of a lab-built MRI coil is provided in this portion of the appendix.

Interdisciplinary research training is also a primary component of the scope of work. The fMRI facility has already conducted three workshops for the faculty and research staff at the University. One was a workshop on the basics of fMRI, another on the design and construction of RF coils, and the third on the use of specific software tools for the analysis of fMRI data.

Groundwork for the implementation of electrophysiological data acquisition simultaneously with fMRI has been done. Circuit designs for filtering the MRI-induced signals in the electrophysiology leads are to be provided by Professor Nikos Logothetis

of the Max Planck Institute (Tubingen, Germany) and these will be constructed and tested for use in both human and primate studies.

To date, six human subject use protocols for fMRI studies have either been approved or are in the process of review for approval by the University's Human Subject Compliance Committee.

Finally, work on the development of automated and semi-automated edge-detection software has been done in the past year. The objective is to remove and/or reduce user bias and selection in the data analysis process and to provide quantitative and robust methods for image segmentation and parcellation. Also, a fully functional program for the conversion of the industry standard 'DICOM' image files (that most MRI devices generate) to other commonly used image files in data analysis programs has been accomplished.

2002-2003

During the last academic year actual results from the BBMI researchers have begun to put together the complex story of how networks are developed in areas ranging from auditory perception to cognitive control. We are approaching this task in many diverse ways. An example of our strategy is to understand the anatomy of neural networks related to cognition and emotion through imaging of adults performing tasks specifically designed to involve the appropriate brain areas. We then use electrical recording from scalp electrodes and of white matter using diffusion tensor imaging to explore the time course and connectivity of the network. We can use cellular studies in primates and other mammals to study processes that take place within the localized nodes of the network. These studies can also suggest candidate genes, known to be important to aspects of the network, which can then be used to study how genes influence the efficiency of network activation in different individuals and are involved in the development of appropriate networks in infants and children. We are beginning to use knockout mice to help us probe the role of genes within the network. The genes involved in network function can be examined in more detail to understand how they control the proteins that build the physical structure of the network. The reports below illuminate our efforts to explore the physical basis of networks underlying significant normal functions and their disorders.

SENSORY AND MOTOR PROCESSES

The barn owl has a highly developed system for processing auditory signals. The study of barn owls has also been an important model for analyzing signals used in human language. A major aspect of auditory perception is localizing the signal in space in order to direct attention to the appropriate source. Takahashi and colleagues (Bola, Spitzer & Takahashi, 2003) report in the journal *Nature*, a model of how broadly tuned neurons can be used in concert to select very precise locations.

In a related effort, Neville and her associates are examining how precise auditory localization develops in human infants (Wood, et al, 2002) and they study the role visual

input has in the development of auditory localization by comparing the process in sighted people with those born blind. These studies have shown evidence of adaptation of visual areas to processing of peripheral auditory signals (Neville & Bevalier, 2002).

The visual system must figure out what objects are present with often very complex scenes. Margaret Sereno and colleagues (Sereno, et al 2002) used computerized displays to give the impression of depth. They have carried out fMRI with monkeys to reveal the precise but distributed brain areas involved in representing stimuli in three dimensions. They have provided needed anatomical links between human and animals and have shown the importance of 3 D representation, not only for awareness of what stimulus is present in the scene, but also to organize action toward the stimulus.

One the earliest and most important actions that human infants make is to point. Intentional pointing in infants is found during the latter half of the first year and becomes a critical feature in interaction between caregiver and infant often called joint attention. Lee and Van Donklear (2002) report that it is possible to create temporary disruptions of the network that controls pointing by stimulation over both dorsal and ventral occipital area in the general areas where Sereno showed 3D vision is computed. In a behavioral study, Dassonville & Bala (2003) find that both ventral and dorsal visual systems are normally involved in responses to common visual input. They explore the effects of a visual illusion and show that both reaching and identification are influenced in the same way by the illusion. These studies suggest important commonalities between the networks for perception and action that will have to be reflected as we work to understand how genes and experience influence these early developing functions.

ATTENTION AND COGNITIVE CONTROL

The study of mechanisms of selection and volition have become important topics for linking cognitive, neurophysiological and genetic studies. Oregon is playing a central role in this effort. Recent studies have provided an anatomical basis for many selective functions and developed important animal models for determining their mechanisms.

Voluntary contro.l For many years psychologists have sought the mechanisms by which one can control the access of memory to consciousness. This fall Michael Anderson (Anderson, et al, 2003) will report results showing that the instruction to avoid consciousness of a memory both reduces the success of later recall and activates a specific network of prefrontal cortex and hippocampus previously related to cognitive control of conflict between brain systems and learning. The studies suggest mechanisms by which trauma, hyponotic suggestion and other poorly understood environmental influences can altar brain networks.

Luu, et al, 2003 have shown that one of the areas involved in Anderson's study (anterior cingulate gyrus) is also important for the detection of error. By recording from multiple scalp electrodes, these authors show that adjacent areas of the ACC are involved in both cognitive emotional regulation that occur as a consequence of the error. Error

detection can be studied easily in adults, infants and animals and thus provides a common method for examining brain areas involved in self-regulation.

It appears that some of these prefrontal regulatory areas are involved in a wide range of tasks that may be unique to human beings. These have been the target areas for a number of new paradigms and models that have been developed by BBMI researchers. For example Ulrich Mayr argues that some of these areas are important when learning requires integration of signal across modalities (Keele, et al, 2003) and Neville and associates report on the activity of these areas during language task (Woods, et al, 2002).

Orienting. The control of orienting to sensory signals has been the strongest model for top down attentional control of sensory input. In this area BBMI researchers have continued to develop important new insights that can connect human and animal models and link to genetic studies.

Beane and Marrocco (in press) report that local infusion of scopolamine into the lateral intraparietal cortex of monkeys alters their ability to orient to visual signals. Marrocco previously found norepinepherine influences the ability to attain the alert state with a warning signal, but does not change orienting. They conclude that under their conditions, activity mediated by muscarinic cholinergic receptors within the intraparietal cortex is necessary for normal covert orienting while influencing norepinepherine transmission influences alerting. These findings are important both in showing the separate modulation of the two attentional networks and in efforts to examine the influence of cholinergic and noradrenergic genes on visual attention.

A paper by Awh, et al, 2003 finds that orienting to objects in space operates at least in part by suppression of the influence of distractors. In a related study using combined ERP/MEG methods Vogel (Hopf, et al, 2002) found sources within the ventral visual stream are involved in a task requires the discrimination of an object from others in the surround. These studies point the way to understanding attentional function in terms of biochemical pathways and provide important clues toward making the genetic analysis.

GENETICS

A goal of our project is to relate the networks studied by cognitive and system neuroscience to the genes and proteins that are involved both in the assembly of common networks and in individual differences in network efficiency. This involves integration of human and animal work within the developing center for mammalian genetics and in the existing center for genomics and proteomics.

Posner and colleagues (Fan, et al, 2003) report that alleles of two genes, known to influence the efficiency of executive attention, also show differences in brain activation within the anterior cingulate when normal adults perform a task involving conflict. Both the MAOA and DRD4 gene influence dopamine transmission. The finding that they change activation in a brain area important for regulating many cognitive and emotional tasks provides an important link between genetic and brain imaging methods. Genes that

relate to individual differences in attention are also likely to be important during the development of this network in early childhood.

Cliff Kentros has been recruited by BBMI to serve as a principal investigator within the new mammalian genetics research center. In his postdoctoral work in the laboratory of Dr. Eric Kandel, Cliff investigated the relationship between neural plasticity and the formation and maintenance of a hippocampal representation of an environment with long-term unit recordings from behaving rodents. His latest work found that the stability of a hippocampal representation of an environment requires selective attention to the available spatial cues and depends upon dopaminergic neurotransmission. These findings suggest important links between attention and memory and provide a powerful animal model for the exploration of the physiological and genetic basis for both of these highly interactive cognitive processes. Trained in molecular biology as well as electrophysiology, Cliff is also helping to set up a core facility for the generation of transgenic mice via pronuclear injection which should be operational by the end of the calendar year.

Two recent projects take genetic behavior links even further. David Grandy, at Oregon Health Sciences University and now an adjunct professor in our new Mammalian Genetics Center, has created a mouse in which the DRD4 gene is deleted. This gene is important in executive attention and attention deficit disorder and its deletion results in signs of hyperactivity and learning deficits (Rubenstein, et al, 2001; Falzone, et al, 2002). Together with Marrocco, he proposes to examine how this deletion influences specific attentional networks in this knockout mouse model and Kentros plans to record electrical activity from cells in these mice.

John Postelthwait has found that to a surprising degree the genetics of the zerbrafish preserves aspects of chromosome organization found in the human (Fredriksson, et al, 2003. He is currently examining the stickleback fish as a possible entry into understanding the genetic basis of aggression. Genes controlling the construction, connectivity and activities of specific brain regions detect and interpret sign stimuli for aggression and mediate motor output. He expects to explore which genes are involved, the brain regions in which they act and what the genes do within these brain regions.

Genomic approaches are well-suited to assay the complex gene networks that underlie the complexity of the brain. Chris Doe has used DNA microarrays and bioinformatics to catalog the genes that make glia, a distinct cell type within the brain. His lab is currently working to dissect the genetic pathways that form various types of neurons using a type of DNA microarray produced only at the University of Oregon genomics facility. Eric Johnson's lab has found that diverse physiological stresses—heat, heavy metal poisoning, low oxygen, caffeine, nicotine and carbon dioxide cause profound changes in gene activity, including a core group of genes that are activated by nearly all stresses. Janis Weeks' lab is working to understand the interplay of hormone signaling pathways and programmed cell death in the nervous system of *Manduca sexta*. Her lab has dissected out the neuromusculature from body segments that experience neuronal cell death due to hormonal signals and compared the gene expression signatures to segments

that retain neuron activity. These experiments were possible due to the microarray production equipment and robotics of the genomics facility, which has created DNA microarrays of five different species in the first year of its operation.

APPLICATIONS

Sharing research. A critical part of modern brain research has been the development of mechanisms by which results obtained in one laboratory can be widely shared. The Zfin project is a large informatics project that allows access to the latest research data on zebra fish genetics (Sprague, et al, 2003). The web-based system has a very flexible and easy to use interface that can allow access to the information by a wide range of users. This is a notable contribution to the goal of shared resources for the world's scientists.

Because of the extremely large data sets developed from fMRI and high density electrical recording, new computer technology is required to store the results and compute relationships between the activations developed by the two methods. The computer methods needed for carrying out these innovations involve massively parallel computation. Maloney & Shende (2003) have explored the needed computer facilities and software. Together with colleagues at BBMI they have recently received a million dollar equipment grant from the National Science Foundation to implement these innovations within the BBMI program at Oregon Medical applications.

Medical. Rod Capaldi has been using proteomic approaches to characterize the entire collection of proteins (the proteome) in human heart mitochondria (Taylor, et al, 2003a). Capaldi and colleagues have discovered that oxidative damage to the mitochondrial electron transport protein "Complex I" leads to neuronal cell death and the resulting neurodegeneration associated with diseases such as Parkinson's and Alzheimer's diseases (Taylor, et al, 2003b; Murray, et al, 2003a). It is anticipated that this methodology will lead to robust new clinical diagnostic tests as well as specific drug therapies for the corrections of these disorders.

The NeuroInformatics Center (NIC) proposes to design and develop a pilot telemedicine test bed that will link remote locations where EEG measurement experiments are conducted to a central facility where the EEG data will be analyzed. The test bed will be built on a distributed computing platform and will utilize the internet for transferring of EEG and MRI data to the center and results to medical specialists. The project will be done jointly between the NeuroInformatics Center and Electrical Geodesics, Inc. (EGI) which markets dense-array EEG systems. The plan is to implement a prototype computational grid between the NIC and EGI several medical service sites.

The van Donkelaar lab has recently received two grants to examine aspects of functional recovery from either stroke or concussion. In the stroke project they use fMRI to examine how constraint-induced therapy induces changes in the patterns of activation during limb motion. The goal is to relate the degree of handedness prior to the stroke to the magnitude of the asymmetry in cortical activation before and after therapeutic

intervention. This may have implications for the extent to which therapy is effective. In the concussion project they have demonstrated using the attention network task that the largest deficits are in the executive control of attention rather than in the orienting or alerting components. Measuring these effects over the course of a one-month recovery period should help in the understanding of the recovery process.

Another new project to be initiated this summer involves the long-term effects of illicit drugs on neural networks. Drs. Ray Nunnally and Tom Dishon will begin a collaboration to use fMRI to examine a cohort of adolescents involved in a long-term longitudinal study of at risk youth.

Education. Michael Posner is involved with the 22 developed countries under the Organization for Economic Cooperation and Development (OECD)to create a website embodying the results of brain research for the acquisition of literacy and numeracy (McCandliss & Posner, 2003). A prototype site in English to be hosted on the OECD website, should be in place by early next year. The site will include information on relevant brain research and contain interactive interventions based on imaging studies for attention training, literacy and numeracy. Expansion to other languages will follow after we gain experience with the prototype.

2003-2004

This report covers our progress in the BBMI program during the academic year 2003-04. During this year we inaugurated our new Center for Mammalian Genetics and recruited new faculty members in that field and in Cognitive Neuroscience. Results from our group have been featured in *Science*, *Nature* and *Neuron*. We are currently advertising for the new postdoctoral program within BBMI.

We have continued our progress in the Lewis Center for neuroimaging, cognitive neuroscience and neuroinformatics and the development of our infrastructure for proteomics and genomics. Highlights are outlined below with a list of new papers at the end.

GENETICS

Our efforts to link human behavior to underlying genes are now centered on studies of fish, mice and humans. Since the genes are similar between these organisms we can often choose the organism to study based upon how easily a specific question can be answered.

Fish. Discovering the functions of the tens of thousands of genes in the human genome is a required step for understanding human biology and disease, including memory and behavior. Genetic model organisms, such as zebrafish, play a critical role in this discovery process, because genetic analysis can connect gene sequence and function.

Model organism databases, like Zfin (Sprague, et al, 2004), provide tools required to make this connection.

Zebrafish has emerged as a premiere model organism because powerful techniques allow efficient generation and recovery of zebrafish mutations affecting genes that regulate developmental patterning, organogenesis, physiology and behavior. Recent advances make it easy to study gene function in transgenic zebrafish and with antisense oligonucleotides. The functions of many of these genes are conserved among vertebrate groups. Thus, analysis of zebrafish mutations provides insights into gene functions in other vertebrates, including humans.

Zfin serves as the community database resource for the laboratory use of zebrafish. It develops support and tools for integrating zebrafish genetic, genomic and developmental information (Henrich, et al, 2004) and maintains the definitive reference data sets of zebrafish research information. The Zfin database links this information extensively to corresponding data in other model organism and human databases to facilitate the use of zebrafish as a model for human biology.

Working together with the Lewis Center for Neuroimaging, Postelthwait and his associates (see Smith, et al, 2004) have succeeded in designing a coil that will allow high resolution imaging of the brains of stickleback, zebrafish and other fish. One reason this is of great importance is the wide applicability of genetic findings with zebra-fish to other species including mammals discussed above. A second reason is that the Postlethwait group has been able to demonstrate the importance of single genes in evolutionary adaptation of a fish, the three spined stickleback. Ocean going stickleback have many spines that are missing in fresh water version of the fish. The research examined fish from several Alaskan lakes and ocean going varieties (Cresko, et al, 2004). The authors asked whether the genetic adaptations, found between these fish populations, could better be explained by changes of a few genes or whether many genes were necessarily involved. It was found that much of the change in the loss of armor plates in the lake fish could be explained by a single gene. The change from ocean to lake dwelling apparently created strong selective pressure for adaptation and these were met by simple underlying genetic changes.

The stickleback has been an important fish for behavioral studies of aggression. The change in armor found in the morphology suggests changes in the behavior of the fish in order to fit the new lightly armored versions. Postlethwait's group is now studying the molecular biology that might underlie changes in the aggressive behavior the fish.

Mice. Cliff Kentros has developed a model system in the mouse for examination of the relation of attention and memory (Kentros, et al, 2004). It was found that the activity of the location specific cells in the hippocampus depends upon engagement in a spatial task. It is assumed that attention to the spatial task is the critical factor in obtaining activation of the cells that code location. Kentros is currently working together with Marrocco who has developed specific tasks for different attentional functions (Beame & Marrocco, 2004) in order to see what aspects of attention are critical for hippocampal place cell

activation. Kentros and colleagues (Agnihotri, et al, 2004) also reported that consolidation of memory by the hippocampus is dependent upon protein synthesis, since blocking such synthesis blocks long-term, but not short-term retention of new, but not old locations. Thus protein synthesis seems critical for consolidation, but not short-term memory or recall of already consolidated memories.

Kentros is also working on the production of genetically modified mice designed for the dissection of the functional elements of neuronal circuits in vivo. The goal is the temporally regulated expression of a dominant negative transgene in a single neuronal cell type, enabling specific elements of neuronal circuits to be turned off during electrophysiological recordings of intact animals. This is achieved by using a novel combination of existing transgenic technologies to "subtract" expression pattern of one promoter from another, maximizing anatomical specificity. He has recently succeeded in generating the first genetically modified mice at the University of Oregon. Success in this venture would allow the analysis of the types of neural circuits discussed at the human level below.

Humans. Ed Vogel, in a recent issues of the journal *Nature* (Vogel & Machizowa, 2004), report a consistent component of the scalp recorded EEG that reflects difference among individuals in the size of working memory for sets of visual items. In his behavioral studies, Vogel finds individual differences in the ability to report simple visual items (colored circles) that range from about 3 items to 7 items. As the size of the memory gets larger so does the amplitude of the lateralized event related potential component. This finding provides a strong electrical sign of an individual's capacity. Previous studies of Ed Awh have shown that this form of working memory draws upon the capacity to switch attention from location to location, which has been linked to cholingergic genes. Ed Vogel is planning to investigate the role of these and other genes in determining the size of visual working memory.

Ed Awh, in work reported in our previous report, has studied the neural system underlying visual search for a target in the presence of distrators. He has been working with Marrocco using the same task with persons who are diagnosed with attention deficit hyperactivity disorder. Current work has connected this disorder with alleles of the dopamine 4-receptor gene and Marrocco has been working with a mouse carrying a targeted deletion of this gene. Initial behavior with indicates that ADHD subjects appear to show a large deficit in their ability to process target in noise, while their ability to process targets in the absence of noise does not show any detectable differences from the control persons. This could provide another link between studies of mice, which have been manipulated genetically and an important human disorder.

The findings linking specific genes to neural networks studied in humans have led the cognitive neuroscience group to propose a center designed, in part, to link cognitive measures of individual differences to genes. This center will include a group of 200 normal subjects who have been run in a wide variety of cognitive tasks of attention, working memory and suppression. They will be genotyped for candidate genes using the facilities provided by the laboratory of Eric Johnson. Efforts will be made to relate the

genes to individual differences in questionnaires and cross-task cognitive operations. By measuring a variety of temperamental and personality characteristics of these subjects an attempt will also be made to determine how individual differences related to cognitive and affective disorders (e.g. anxiety, schizotypy) may relate to candidate genes identified in studies of schizophrenic patients and of normal attention.

Imaging of Cognitive Functions

Tool Use. Scott H. Johnson-Frey will be joining our cognitive neuroscience group this fall. His most recent work has focused on identifying brain mechanisms underlying complex manual behaviors, most notably tool use. Scott's lab uses functional and structural MRI techniques to identify distributed networks associated with particular behaviors of interest. Hypotheses concerning the specific cognitive operations performed within particular brain regions are then evaluated in one of two ways. MRI-guided transcranial magnetic stimulation (TMS) can be used in conjunction with psychophysical testing to determine the behavioral consequences of disrupting briefly the functions of a given cortical location. Neuropsychological testing may be used to determine the effects of regional damage. Scott is also part of a multi-institutional effort to identify critical differences in brain organization and cognitive function between humans, chimpanzees, and other primate species through use of techniques ranging from neurogenomics to behavioral testing.

Perception, Attention and Memory

Michael Anderson and colleagues (Anderson, et al, 2004) reported, in a recent issue of *Science* that people could be instructed to suppress the storage of new associations in memory. When they do so, they not only show reduced memory of the suppressed association, but they have reduced activation in the hippocampus, which is a crucial node of the network for storing memories and increased prefrontal activation in areas related to inhibitory control. These findings provide a strong experimental model for repression of memories. Johnson & Anderson (2004) have found that a similar inhibitory process may be important in normal forgetting of semantic facts.

In a review of the literature on the conditions for visual awareness Mayr (2004) argues that activation of the anterior cingulate, an important node of cognitive control, requires a conflict of which the person is consciously aware and is not triggered if the conflict remains outside of awareness. In a recent paper (Luu, et al., 2003) anterior cingulate activation has been shown to arise in the form of a theta rhythm in anticipation of feedback. Activity in this region was potentiated in depressed individuals in comparison with controls (Tucker, et al, 2003). Since individual differences in anterior cingulate activation have been related to several candidate genes (Posner, in press), it may be possible to predict which people are most likely to exhibit activation in this area under conditions of ambiguous exposure or enhanced feedback.

Several new findings relate to the way attention may interact with visual displays to influence the material that people can report. Awh and colleagues (Awh, et al, 2004) show that the attentional blink, that serves to impair the report of a brief alphanumeric stimulus, does not impair face perception. This suggests that attention may be inhibited from processing two stimuli of the same category but not when they are of categories that have different visual system localizations. Dassonville, et al (2004) found that a visual illusion of location induced by a surrounding frame (Roelofs effect) is due to a perceived shift of the midline of the object toward the frame.

The Neville lab has identified different neurocognitive systems that display different degrees of neuroplasticity throughout life (Capek, et al, 2004; Sanders, et al, in press; Roeder and Neville, 2003; Sanders and Neville, 2003). They are conducting developmental studies of these different neurocognitive systems in children, in part to try and elucidate factors that determine different levels of neuroplasticity (Mills, et al, in press; Mitchell and Neville, in press; Coch, et al, in press (nonrhyme). The lab is initiating a series of studies to assess the effects of different interventions on neural and cognitive development.

Clinical Studies and Treatment

The van Donkelaar lab has initiated two projects examining the changes in brain activation patterns in patients who are recovering after brain damage. A project funded by the Centers for Disease Control, has demonstrated that patients with a concussion have distinct attentional deficits as assessed behaviorally with the Attentional Network Test (ANT). This test separate components of attention related to attaining the alert state, orienting to sensory events and monitoring conflict between responses. The orienting and conflict components of attention appear to be affected by concussion, but not the alerting component. A current project is to examine whether these behavioral deficits have correlates in the pattern of brain activity in patients with concussion as assessed with fMRI. In addition, magnetic resonance spectroscopy is being used to determine whether the neurochemistry of the brain is also altered in concussion and whether these alterations are confined to the areas underlying the behavioral deficits we have previously observed.

A second project, funded by the American Heart Association, examines how patients who have suffered a stroke recover function following an intensive form of physical therapy called constraint induced therapy. The fMRI is used to discover how this functional recovery is correlated with alterations in brain activation patterns. Furthermore, the extent of activation is being related to the degree of handedness prior to the stroke. The prediction is that the degree of handedness will determine the capacity for both functional recovery and brain activation alterations.

A project to examine the effect of drug use by adolescents on brain activation, is being developed jointly by Ray Nunnally and Tom Dishon. A recent paper (Wills & Dishon, 2004) reviews the determinants of substance abuse by adolescents. Current research has suggested that smoking behavior by adolescents may be related to efforts to

improve their attention. Considerable evidence in the literature suggests that smoking can improve some aspects of attentional functioning. A study by Gardner & Dishon currently in process suggests changes in executive attention, as measured by the attentional network test (ANT), is related to tobacco use. Current work is examining the effects of cannabis use, both on behavior aspects of attention measured by the ANT, and on brain areas related to attention.

Brain and Education

A committee on Brain and Education has been developed to foster connections between BBMI and the College of Education on the study of neural networks related to achievement in school settings. A plan to hold a statewide workshop on Brain Plasticity and Education May of 2005 has been developed. The planned speakers include Helen Neville, Michael Merzenich and Elizabeth Spelke. An interactive TV link between Eugene and Portland is planned with delayed connections in LaGrande, Roseburg, Bend and other centers. These connections are designed to foster participation in teachers of K-12 interested in the neuroscience related to education. The committee will shortly issue a paper describing research and outreach programs in the area of Brain and Education at the University of Oregon.

Genomics and Proteomics

Much of the development of the brain and aspects of behavioral control are regulated by gene expression. The genomics facility developed by Eric Johnson has developed DNA microarrays for measuring gene expression on a global scale in eight model organisms in the past two years. These tools have furthered BBMI-related research in a number of labs, and are poised to produce new results in a number of others. Their use in conjunction with cognitive neuroscience was discussed above.

Chris Doe used the microarrays developed by Johnson in a study describing the genetic program to create glia cells, which support nerve cell activity (Freeman, et al, 2003). The Doe and Johnson labs are collaborating on a more complex microarray that allows them to identify the regulatory network controlling gene expression. The Doe lab has been using this new microarray to uncover the logic circuit that produces one type of nerve cell versus another. The Johnson lab has examined the way different genes are targeted by the same regulator in different tissues—the brain versus the respiratory system. The Johnson lab has also completed a study using microarray to study of how different stress-regulated pathways regulate common and specific response genes. Janis Weeks has used microarrays to identify genes in the neuromusculature junction that respond to pulses of hormone during development, and how differences in the response to hormones can lead to a decision for a neuron to live or die.

Several other projects are underway or starting soon. Bill Bradshaw is developing a microarray to dissect out the gene expression changes underlying how behavior changes in response to the seasons and length of day. Phil Washbourne and Cliff Kentros, are starting mouse-based microarray projects to examine gene expression during brain

development and memory. Patrick Philips and his lab are collaborating with the Berglund and Bowerman labs to create a C. elegans microarray, which will be used to help map behavioral differences between natural populations.

Neuroinformatics

The Neuroinformatics Center (NIC), has completed installation of the ICONIC grid which will provide high performance computing to BBMI. The ICONIC grid integrates three advanced IBM computing architectures on a shared area network multiple terabyte storage base, linked by microchannel fiber. This system will be used by BBMI to implement integration of information from hemodynamic, electrical and optical recording with much greater precision than was previously possible.

There are now two primary software development projects being implemented on the ICONIC (integrated cognitive neuroscience) Grid. The first project is statistical decomposition of dense array electroencephalographic (EEG) signals. The initial goal for this project is extraction of noncephalic artifacts, including eyeblinks, eye movements, and cardiac potentials, from the EEG record. The second project is computational modeling of the electrical properties of the human head, including both electrical and optical transmission. Currently the NIC has used independent component analysis (ICA) to remove artifacts due to eye blink and other noncephalic sources.

The NIC continues its development of a prototype system for telemedicine including applications to both military and civilian emergency medicine. Current work focuses on application to stroke. NIC is proposing to develop a 512 channel system that will combine electrical and optical imaging of the human brain (to be called HALO for head accessed laminar optoeletrics). The optical signaling uses a new technology that has been developed to achieve high signal sensitivity through the integration of avalanche photodiode detectors with laser diode optical sources. The Center plans to submit a proposal to the Defense University Research Instrumentation program (DURIP) to continue these developments.

Workshops

Three workshops were successful held during 2004.

January 15-16. Temporal coding in relation to imaging studies.
On Thursday evening Ron McKay provided an update on the creation of brain tissue via the use of stem cells. He described his efforts to develop active dopamine cells to a large and excited audience. On Friday afternoon Dr. McKay and Hillyard met with faculty graduate students and postdocs to review work in BBMI related to their expertise. A number of presentations were made and a lively discussion ensued. Friday afternoon Dr. Koretsky presented his work on temporal coding using MRI method. Following his presentation, Dr. Hillyard presented combined fMRI-EEG methods for tracing the time course of neural activity.

April 16. The dedication of new mammalian genetics center.
An afternoon session allowed members of our group including Drs. Kentros, Marrocco, and Johnson to discuss with our guests work ongoing and anticipated in the mammalian genetics program. Our guest speakers, Dr Steve Soumi (primate behavior and genes) and Dr. Alcino Silva (mouse genetics) presented in the afternoon.

May 21-22. Brain, Learning and Curriculum.
Friday evening commenced with a presentation on dyslexia by Drs. Sally and Ben Shaywitz. A large audience of faculty, students and K-12 teachers and administrators were present. The next morning Dr. Dave Premack discussed the implications of his work on original intelligence for the design of a rational school curriculum. As a result of this highly successful workshop BBMI has set up a new Brain and Education committee to review and coordinate work between the College of Education and BBMI on the topic of brain and education.

Anticipated Programs

Fall, 2004. Lewis Center Workshop
It is anticipated that a fall workshop will review the development of coils for animal imaging of mice and fish and discuss the development of a new 11.7 tesla animal scanner.

February, 2005. Neuroinformatics Workshop
This will cover opportunities developed from the installation of the ICONIC grid on the campus. It will also consider some of the progress in telemedicine including research on stroke and epilepsy.

April, 2005. Genomics & Proteomics
Discussion of the new mass spectrometer as well as the new programs in genomics including a number of animal models.

May, 2005. Brain Plasticity and Education
A joint statewide program with the Oregon Health Sciences University to be help in Eugene with interactive TV to Portland sites. The speakers will be Helen Neville, Elizabeth Spelke and Michael Merzenich. They will cover how new research in brain plasticity can be applied to the learning of school subjects.

III. Research Accomplishments

- Purchase and installation of a 3 tesla brain imaging system.
- Demonstration of state-of-the-art human and non-human subject MRI results on a routine, day-to-day basis.
- Establishment of the capability to design and fabricate purpose-built MRI (RF) coils on an 'everyday' basis.
- Implementation and use of the MRI-controlled triggering of visual stimuli to subjects in the MRI magnet and acquisition of fMRI data.
- Publication of significant results on perception, attention and learning as reported in various publications below.
- Obtained a one million dollar NSF instrumentation grant and installed the new ICONIC (integrated computing in cognitive neurosciene). Obtained additional equipment as a result of collaboration with IBM.
- Established a new mammalian genetics center. Recruited a new faculty member, adjunct visiting professor and technical staff to begin work on the Mouse Neuroanatomy Project.
- Developed proposal for a new Cognitive Neuroscience of Attention Center to synthesize research on imaging and genetics of attention and cognitive control.
- Created a Center for Genomics and Proteomics with state of the art facilities for robotically controlled genome scans and begun extensive collaborations with several animal models
- Have purchased a will install shortly a state of the art mass spectrometer for carrying out proteomic studies

IV. Reportable Outcomes

- We have obtained grant funding from NSF for the ICONIC grid high performance computer system and erected a close cooperation with IBM, who have contributed additional equipment.

- We have prepared a Center grant from NIH for Attentional Control Across Cognitive Domains to link cognitive neuroscience research to genetics

- Dr. Ray Nunnally has applied for a NIDA grant for work on addictive disorders.

- A grant request to the Keck Foundation for support of work in mammalian genetics has passed the first round and will be evaluated in December.

- We have developed a collaboration with OHSU in our new mammalian genetics center.

- A statewide collaboration with OHSU on Brain and Education outreach has been developed by our Brain and Education Committee.

V. Conclusions

Over the past four years the University of Oregon with support from DOD has established a world center for the analysis of genetic and cellular mechanisms underlying human brain function. In the Lewis Center for Neuroimaging has completed and underway many studies revealing neural networks related to attention, memory, perception and learning. These are dependent on the successful installation of the 3T Scanner and the development of the ICONIC grid for integrating EEG and fMRI signals. Through the establishment of a genomics facility and a mammalian genetics center we are attempting to link elements of these networks to underlying genes and proteins. While these efforts are on-gong we have already begun to apply them in many domains. These include studies of brain injury patients, telemedicine, and work on brain and education. This project has realized many of its initial goals, but much work remains to be done to employ the new tools to foster integrative research and to further the applications we have begun.

VI. Publications

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